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REVIEW

Hyperkalemia management: a multidisciplinary expert panel's perspective on the role of new potassium binders

Cândida Fonseca[1,2] · Cristina Garagarza[3,4] · Gil Silva[5] · Graça Caires[6] · Irene Marques[7,8] · José António Lopes[4,9] · Patrícia Branco[10] · Rui Alves[11,12] · Aníbal Ferreira[2,13]

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Abstract

Hyperkalemia is a potentially life-threatening condition frequently encountered in clinical practice, particularly among patients with chronic kidney disease, heart failure, diabetes, and hypertension and those undergoing treatment with renin–angiotensin–aldosterone system inhibitors (RAASi). The management of chronic and acute hyperkalemia is complex and requires timely intervention to prevent severe complications such as cardiac arrhythmias and sudden death. Traditional therapeutic approaches to chronic hyperkalemia, including dietary potassium restriction, use of diuretics, and administration of cation-exchange resins like sodium polystyrene sulfonate, often suffer from limitations like gastrointestinal side effects, variable efficacy, delayed onset of action, and RAASi treatment discontinuation. In recent years, the development of new potassium binders, specifically patiromer and sodium zirconium cyclosilicate (SZC), has revolutionized the management of hyperkalemia. Patiromer, a non-absorbed polymer, binds potassium in the gastrointestinal tract in exchange for calcium, thus facilitating its excretion. SZC operates by exchanging sodium and hydrogen ions for potassium, leading to efficient potassium removal. Both agents have demonstrated rapid and sustained reductions in serum potassium levels, coupled with favorable safety and tolerability profiles, in multiple clinical trials. This review article, authored by a multidisciplinary group of Portuguese experts in hyperkalemia management, provides an in-depth analysis of the efficacy and safety of current therapeutic strategies and highlights the clinical potential of new potassium binders. The introduction of patiromer and SZC offers significant advantages over traditional therapies, providing effective and better-tolerated options for patients. The review highlights the role of these novel agents in contemporary hyperkalemia management and calls for ongoing research to further refine treatment protocols and improve patient outcomes.

Keywords Hyperkalemia · Patiromer · Sodium zirconium cyclosilicate · Chronic kidney disease · Heart failure · RAASi therapy

Introduction

Hyperkalemia (HK) is a common, potentially life-threatening condition characterized by elevated serum potassium levels (> 5.5 mmol/L) due to increased intake, decreased excretion, or intracellular potassium release [1]. Acute HK requires immediate treatment to stabilize the myocardial cell membrane, shift potassium intracellularly, and reduce total body potassium [2, 3]. Chronic HK develops more slowly, posing increased morbidity and mortality risks. HK is prevalent in patients with chronic kidney disease (CKD), heart failure (HF), diabetes, and hypertension, especially those on renin–angiotensin–aldosterone system inhibitors (RAASi), which exacerbate potassium retention [2, 4–7]. Often CKD and HF coexist and lead to cardiorenal deterioration [8–10], further compounded by RAASi, leading to increased HK risk [4, 11, 12]. Even mild HK (5.0 to < 5.5 mmol/L) can result in increased mortality and morbidity [13, 14].

RAASi are a mainstay of CKD, HF, diabetes, and hypertension management. However, its use implies a thorough monitoring of potassium levels and treatment optimization [2, 4, 15, 16]. For moderate (5.5 to 6.0 mmol/L) or severe (> 6.0 mmol/L) HK, temporarily discontinuing RAASi may be necessary, although this poses a risk of disease progression [4, 11, 12, 17, 18]. Current guidelines of HK management recommend potassium-lowering treatments simultaneously with RAASi [2, 4]. Classic potassium-binding agents such as sodium polystyrene sulfonate (SPS) have

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long-standing and extensive use, although they are badly tolerated and there have been several case reports of severe gastrointestinal injury [19–21]. Patiromer and sodium zirconium cyclosilicate (SZC), are new, well-tolerated options for effectively normalizing serum potassium and preventing HK recurrence [22, 23].

In this article, a multidisciplinary panel of Portuguese experts in cardiology, nephrology, internal medicine, and nutrition, with experience in HK management, convened to provide a comprehensive overview of HK, focusing on current management strategies, including dietary modifications and pharmacological interventions. Specifically, we conducted a state-of-the-art review of patiromer and SZC, assessing their efficacy, safety profiles, and clinical implications. By highlighting the latest advancements in HK management and offering insights into the comparative effectiveness of these potassium binders, we aim to equip cardiologists, nephrologists, and internists with the essential knowledge for optimal patient care and improved clinical outcomes.

Pathophysiology

Normal potassium homeostasis involves a delicate balance between intake, excretion, and distribution between intracellular and extracellular compartments, with 98% of potassium residing inside cells to maintain resting plasma membrane potential [24]. The kidneys play a crucial role in this balance through filtration, reabsorption, and secretion, with aldosterone regulating potassium excretion via a feedback mechanism involving sodium–potassium pumps (Na + /K + -ATPase) [1, 24]. HK arises from reduced renal excretion, intracellular potassium shifts, or increased intake [5, 25]. Renal-mediated HK can result from altered nephron flow, dysregulated aldosterone secretion, and dysfunction in potassium secretory pathways, commonly seen in conditions like HF, cirrhosis, acute kidney injury (AKI), and CKD [1, 5, 25]. Hypoaldosteronism, often due to adrenal insufficiency or diabetic nephropathy, also impairs potassium excretion [1, 4]. Transcellular potassium shifts, influenced by factors like elevated plasma osmolality, insulin deficiency, and metabolic acidosis, contribute significantly to HK [1]. Elevated plasma osmolality, often seen in uncontrolled diabetes, creates a gradient that causes potassium to exit cells along with water [1]. Insulin deficiency or resistance, also common in diabetes, reduces potassium uptake by cells [25]. Metabolic acidosis, frequently associated with renal dysfunction, drives the exchange of extracellular hydrogen ions for intracellular potassium, exacerbating HK [1]. Additionally, since 98% of total body potassium is intracellular, conditions that increase cell turnover, such as rhabdomyolysis, tumor lysis syndrome, or red blood cell transfusions, can lead to HK [5].

Medications, particularly those affecting the RAAS (angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), are frequent HK contributors, especially in patients with renal dysfunction and/or heart failure [25, 26], although they play a vital role in the treatment of various cardiorenal conditions [1, 4, 11, 12]. Additionally, medications such as trimethoprim, heparin, beta-blockers, digoxin, and nonsteroidal anti-inflammatory drugs are recognized contributors to HK [25]. Constipation, excessive dietary intake of potassium-rich foods, and/or ingestion of sodium chloride substitutes are rarely the cause of HK in healthy individuals. However, when combined with comorbidities or certain medications, the risk of HK escalates [5, 7, 27]. In these susceptible individuals, the appropriate moderation of dietary potassium intake is recommended [4].

HK impacts various organ systems, primarily the heart and neuromuscular function, leading to potentially life-threatening arrhythmias and neuromuscular symptoms [1, 5, 10, 28]. It can also exacerbate renal dysfunction, creating a vicious cycle of potassium retention and imbalance [4, 29].

Epidemiology and clinical impact

Global estimates of HK incidence and prevalence vary widely due to differences in study populations and potassium thresholds. A meta-analysis by Humphrey et al. reported a 6.3% prevalence and an incidence of 2.8 cases per 100 person-years in adults, with higher rates in individuals with comorbid conditions such as end-stage kidney disease (ESKD) (21.5%), kidney transplant recipients (21.8%), AKI (24.3%), and HF patients (6.5%) [30]. Kovesdy et al. highlighted kidney disease as a primary predictor of HK, showing a nearly linear correlation between lower estimated glomerular filtration rate (eGFR) and increased HK incidence, with a three-fold rise in HK for every 15 mL/min/1.73 m^2 decrease in eGFR in stage 3 CKD or higher [31]. Among patients with HF, the incidence of HK is up to 40% in chronic HF and 73% in CKD over follow-up durations of 1 year [32].

HK imposes a significant socioeconomic burden, leading to higher emergency department visits, hospitalizations, and intensive care unit admissions, particularly when accompanied by advanced CKD, HF, or diabetes [14]. A large observational study found that the predicted risk of all-cause mortality for individuals with HK was 7.6-fold higher in those with all three comorbidities and 3.3-, 3.5- and 1.6-fold higher in those solely with HF, CKD, and diabetes, respectively [5, 13]. RAASi treatment doubles the risk of HK compared to untreated controls, often necessitating dose reduction or discontinuation to manage HK, despite guidelines recommending reinitiation post-resolution to avoid depriving patients of critical medication

[4, 33, 34]. Nevertheless, most patients are not reintroduced to therapy during the subsequent year [17, 35].

Reduced RAASi dosing below the maximum recommended increases the risk of adverse cardiac events and mortality in CKD and HF patients [34, 36, 37], creating a feedback loop where RAASi therapy improves long-term prognosis but worsens short-term outcomes due to elevated potassium, and HK leads to decreased RAASi use, adversely affecting long-term prognosis [11]. In patients with HF, however, evidence suggests that HK serves as a risk marker for mortality, primarily due to the underutilization of RAASi, rather than being an independent risk factor for mortality [38].

Diagnosis

The clinical diagnosis of HK demands meticulous attention to clinical symptoms, patient background, and laboratory findings, with electrocardiography (ECG) serving as a vital tool for assessing cardiac effects. Identifying HK patients presents a challenge due to the non-specific nature of symptoms, ranging from severe manifestations like cardiac arrest or muscle paralysis to non-specific complaints such as chest pain, weakness, and abdominal discomfort [1, 5, 39]. Serum potassium levels ≥ 5.5 mmol/L are widely acknowledged as indicative of HK [4, 12, 13, 36, 40], but rapid spikes in potassium concentration can trigger severe complications regardless of the absolute value [16, 40]. ECG abnormalities are crucial for assessing the physiological significance of HK, even at serum potassium levels < 6.0 mmol/L [20, 25, 39, 40]. Nonetheless, especially in high-risk patients, the absence of ECG abnormalities should not rule out the presence of HK, and an accurate laboratory-confirmed HK diagnosis should be guaranteed before initiating treatment in stable patients [3, 39]. Laboratory testing should include urine and blood analyses to screen for associated morbidities and treatments, renal function, acid–base status, and potential causes of HK [40]. During the diagnostic process, particularly when interpreting clinical biochemistry data, it is crucial to rule out pseudo-HK in patients without ECG alterations and lacking risk factors for HK [5]. Falsely elevated serum potassium values can occur during or after blood collection and can be caused by hemolysis, leukocytosis, or thrombocytosis or even problems with sample transport, pre-analysis, or contamination [5, 40].

Management strategies

While several guidelines and consensus statements have been developed for HK management [3, 4, 11, 12, 41–44], a universally accepted agreement on best practices remains elusive. HK management spans a continuum, comprising urgent, short-term, and long-term treatment modalities, which are implemented in both inpatient and outpatient settings. Moreover, different management strategies can be employed based on whether the patient presents with acute or chronic HK (Fig. 1) [16].

Management of acute hyperkalemia

Acute HK is a rapid-onset condition that can quickly escalate to a medical emergency due to its potential to cause life-threatening cardiac arrhythmias [43]. Treatment depends on the potassium level, HK duration, comorbidities, and end-organ injury [3]. Emergency treatment is typically recommended for serum potassium levels ≥ 6.0 mmol/L, regardless of ECG changes [3, 4, 43].

Acute HK management recommendations involve a multifaceted intervention (Fig. 1). Firstly, stabilization or reversion of the HK-related ECG alterations, arrhythmias, or cardiac arrest can be achieved by intravenous calcium gluconate or calcium chloride administration, to counterbalance the effect of potassium on myocytes. The effect of the infusion starts in 1–3 min and lasts 30–60 min [3, 5]. Secondly, to shift serum potassium into the intracellular space through the activation of Na + / K + -ATPase pump, insulin is administered intravenously, and the onset of effect occurs within 30–60 min and can last up to 6 h [3, 5, 42]. To prevent hypoglycemia, glucose is administered with insulin, under close monitoring for several hours [3, 5]. Beta-2 agonists like albuterol also promote the translocation of potassium into the cells by activating Na + /K + -ATPase pump, but with a shorter duration of action [3, 5, 42]. Finally, to eliminate excess serum potassium, novel oral potassium binders, initially approved for chronic HK, also appear to be safe and effective in the acute HK setting [3, 42, 45].

Despite increasing clinical use, the definitive efficacy of these binders in acute HK is still being studied, with a randomized controlled trial underway [43, 45, 46]. In most cases, acute HK can be effectively treated with a combination of potassium-shifting and elimination strategies. However, persistent HK, particularly in patients with significant renal impairment or ESKD, may require hemodialysis for potassium removal [3, 5, 42]. Identifying the underlying cause of HK is essential to prevent recurrence and ensure comprehensive management.

Management of chronic hyperkalemia

Chronic HK is characterized by persistent high serum potassium levels requiring long-term management, particularly common in individuals with CKD [4, 5, 30], diabetes, or HF [6, 13] and those using RAASi [11, 12, 36, 47].

Initial management includes dietary modifications to reduce potassium intake, particularly in patients with

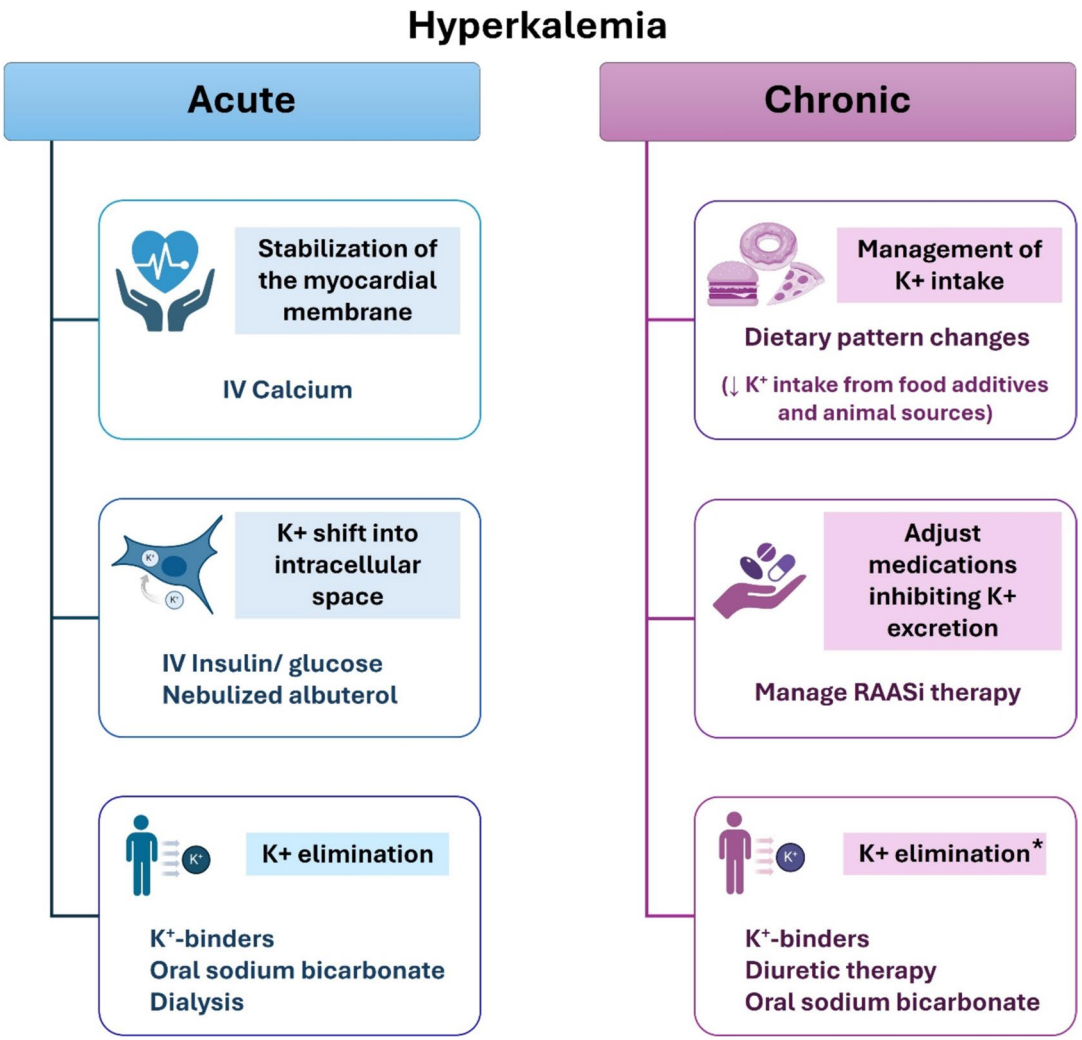

Fig. 1 Management approaches for acute and chronic hyperkalemia. *The implementation of these measures will allow the optimization of RAASi therapy. IV, intravenous; K^+, potassium; RAASi, renin–angiotensin–aldosterone system inhibitors

compromised renal function [4]. However, the impact of dietary potassium on serum levels is only partially understood [24]. Recent studies, such as those involving hemodialysis patients adhering to the DASH (Dietary Approaches to Stop Hypertension) diet, indicate that potassium-rich diets might not increase serum potassium levels and may even lower them due to high fiber content and alkali profile [48]. Medications that affect renal potassium excretion, like RAASi, require careful optimization, potentially involving dose adjustments or alternative therapies. Rather than discontinuing RAASi, associated HK can often be managed with measures to reduce serum potassium [17]. Potassium binders like SPS, patiromer, and SZC help excrete potassium via the gastrointestinal tract [16, 49] and can support continued optimized RAASi therapy [11, 12, 23]. While some guidelines recommend starting potassium binders when serum potassium is ≥ 5.0 mmol/L [2], others suggest a threshold of > 6.0 mmol/L [43] or > 5.5 mmol/L [4, 12]. Other measures useful to reduce levels of serum potassium are oral supplementation with sodium bicarbonate in patients with chronic metabolic acidosis and potassium-wasting diuretics in patients with extracellular volume expansion [43].

Regular monitoring of serum potassium and renal function is critical to prevent complications such as cardiac arrhythmias. KDIGO (Kidney Disease: Improving Global Outcomes) guidelines advise monitoring serum creatinine and potassium within 2–4 weeks of starting or adjusting RAASi therapy, with monitoring frequency tailored to patient comorbidities and medications [4, 16]. Collaborative care among healthcare providers, including nephrologists, cardiologists, dietitians, and primary care providers, is essential for optimal management and to prevent acute exacerbations of chronic HK (Fig. 1).

Table 1 Selected characteristics of the novel potassium binders

Variable	Patiromer [58–60]	SZC [61, 62]
Date of FDA approval	October 2015	May 2018
Date of EMA approval	July 2017	March 2018
Chemical Properties	Cross-linked polymer; patiromer sorbitex calcium	Nonpolymeric; nonabsorbed zirconium silicate
Sodium content	None	80 mg/g
Mechanism of action	Exchanges calcium for potassium; also binds magnesium	Captures potassium in exchange for hydrogen and sodium
Onset of action (earliest timepoint tested until now)	2 h	1 h
Dose	8.4 g QD (oral), titrate up to 16.8 g or 25.2 g QD	10 g TID (oral) for initial correction of hyperkalemia (for ≤ 48 h), then 5 g QOD to 15 g QD for maintenance
Administration	Oral	Oral
Site of potassium binding	GI tract—colon	GI tract—small and large intestine
Adverse effects	GI disorders (abdominal discomfort, constipation, diarrhea, nausea, flatulence), hypomagnesemia	GI disorders (constipation, diarrhea, nausea, vomiting), mild to moderate edema
Drug interactions	Take other orally administered drugs ≥ 3 h before or 3 h after	Oral medications that exhibit pH-dependent solubility should be administered ≥ 2 h before or 2 h after
Contraindications/cautions	Avoid with severe constipation or bowel obstruction or impaction, including abnormal postoperative bowel motility disorders Monitor for hypomagnesemia Patiromer binds many orally administered medications	Avoid with severe constipation or bowel obstruction or impaction, including abnormal post-operative bowel motility disorders Drug interactions: transient increase in gastric pH
Absorption	Not systemically absorbed	Not systemically absorbed
Elimination	Excretion: feces	Excretion: feces

EMA European Medicines Agency, *FDA* Food and Drug Administration, *GI* gastrointestinal, *QD* once daily, *QoD* every other day, *TID* thrice daily.

Management of post-transplantation hyperkalemia

HK is common in organ transplant recipients due to renal dysfunction and medications such as calcineurin inhibitors, trimethoprim-sulfamethoxazole, and RAASi that affect potassium regulation [50]. Managing HK often involves reducing or discontinuing these drugs, which increases risks of infection, organ rejection, and healthcare costs [50, 51]. Management strategies mirror those for acute and chronic HK, focusing on adjusting immunosuppressive regimens, optimizing renal function through hydration and blood pressure management, and dietary potassium reduction [51, 52]. Regular monitoring of serum potassium and renal function is crucial, with timely medication adjustments to prevent recurrence [52]. Emerging potassium binders like patiromer and SZC show promise for chronic HK management in transplant patients, though long-term efficacy studies are needed [50–52]. Effective care requires collaboration among transplant specialists and other medical specialists to create tailored strategies that preserve graft function and ensure patient safety, optimizing outcomes for transplant recipients.

New potassium binders

Classic potassium binders, such as SPS and calcium polystyrene sulfonate (CPS), have been employed in clinical practice for over six decades as a treatment for HK [20]. These non-selective cation-exchange resins also have an affinity to bind magnesium or calcium ions [16] and, due to the variable onset of action (from 1 h to 1 day), are unsuitable for using in acute settings [20]. Despite its long history of use, classic potassium binders are associated with significant side effects, including gastrointestinal adverse effects such as bleeding, constipation, diarrhea, gastric irritation, perforation, intestinal ischemia, or colonic necrosis [19]. Recently, Vidal and colleagues demonstrated through infrared spectroscopy that CPS crystals were deposited in the colon of a CKD patient, inducing colitis [21]. Given these adverse effects and the availability of newer potassium-binding agents with improved safety profiles, the routine use of SPS and CPS has come under scrutiny. Current guidelines generally recommend considering alternative therapies for HK management, reserving classic potassium

Table 2 Summary of patiromer clinical studies for the treatment of hyperkalemia

	PEARL-HF (NCT00868439) [63]	OPAL-HK (NCT01810939) [70]	AMETHYST-DN (NCT01371747) [64]	AMBER (NCT03071263) [76]	DIAMOND (NCT03888066) [77]
Mechanism of action	Patiromer	Patiromer	Patiromer	Patiromer	Patiromer
Study design	Phase 2, randomized, double-blind, placebo-controlled	Two phases: a single-group, single-blind initial treatment phase (ITP) and a Phase 3a, placebo-controlled, single-blind, randomized withdrawal phase (RWP)	Phase 2, randomized, open-label, dose-ranging	Phase 2 randomized, double-blind, placebo-controlled	Phase 3, randomized, double-blind, placebo-controlled
Population	Patients with chronic HF receiving standard therapy	Patients with stage 3 or 4 CKD	Patients with type 2 diabetes	Patients with CKD (eGFR = 25 to ≤ 45 mL/min per 1.73 m^2) and uncontrolled resistant hypertension	Patients with HFrEF
Regimen	Patiromer 30 g/day or matching placebo	ITP: 243 patients received at least one dose of patiromer (18.2 g/day) RWP: A total of 107 patients were randomly assigned to continue patiromer (20.6 g/day) treatment (55 patients) or to switch to placebo (52 patients)	Patients were stratified by baseline serum K + level into mild or moderate HK groups and received 1 of 3 randomized starting doses of patiromer (4.2 g, 8.4 g, or 12.6 g twice daily [mild HK] or 8.4 g, 12.6 g, or 16.8 g twice daily [moderate HK]). Patiromer was titrated to achieve and maintain serum K + level 5.0 mEq/L or lower	Placebo or patiromer (8.4 g/day), in addition to open-label spironolactone (starting at 25 mg once daily)	Patiromer 8.4–25.2 g/day or matching placebo
Previous treatment	ACEI or ARB and a beta-adrenergic blocking agent in addition to spironolactone 25–50 mg/day	Had been receiving a stable dose of ≥ 1 RAASi for ≥ 28 days	ACEI, ARB, or both, with or without spironolactone	Anti-hypertensive medications	ACEI, ARB, ARNI and/or MRA The run-in phase could last up to 12 weeks and was designed to control K + with patiromer (titrated up to maximum of 25.2 g/day) while concurrently optimizing the RAASi therapy
Sample size	105	$n = 243$ (ITP) $n = 107$ (RWP)	304	295	878
Median age (± SD) (years)	67.9 (9.9)	67.4 (8.6)	66.3 (8.61)	70.1 (10.1)	66.8 (10)
Baseline potassium levels mmol/L (± SD)	4.7 (0.2)	5.6 (0.6)	5.3 (0.4)	4.71 (0.42)	4.6 (0.3)
Follow-up	1 month	1 + 2 months	52 weeks	3 months	12 months

Table 2 (continued)

	PEARL-HF (NCT00868439) [63]	OPAL-HK (NCT01810939) [70]	AMETHYST-DN (NCT01371747) [64]	AMBER (NCT03071263) [76]	DIAMOND (NCT03888066) [77]
Primary outcome	Compared with placebo, patiromer had significantly lowered serum K + levels with a difference between groups of − 0.45 mEq/L ($P < 0.001$); a lower incidence of HK (7.3% patiromer versus 24.5% placebo, $P = 0.015$); and a higher proportion of patients on spironolactone 50 mg/day (91% patiromer versus 74% placebo, $P = 0.019$) In patients with CKD ($n = 66$), the difference in K + between groups was 20.52 mEq/L ($P = 0.031$), and the incidence of HK was 6.7% patiromer versus 38.5% placebo ($P = 0.041$)	ITP: The mean (± SE) change in serum K + levels from baseline to week 4 was − 1.01 ± 0.03 mmol/L (95% CI, − 1.07 to − 0.95; $P < 0.001$) RWP: The estimated median change in the K + level from the start to week 4 of the phase was 0.72 mmol/L in the placebo group and 0 mmol/L in the patiromer group, for a between-group difference of 0.72 mmol/L (95% CI, 0.46 to 0.99; $P < 0.001$)	Mean reduction from baseline in serum K + level at week 4 or time of first dose titration: Mild HK: 4.2 g dose: 0.35 (95% CI, 0.22–0.48) mEq/L 8.4 g dose: 0.51 (95% CI, 0.38–0.64) mEq/L 12.6 g dose: 0.55 (95% CI, 0.42–0.68) mEq/L Moderate HK: 8.4 g dose: 0.87 (95% CI, 0.60–1.14) mEq/L 12.6 g dose: 0.97 (95% CI, 0.70–1.23) mEq/L 16.8 g dose: 0.92 (95% CI, 0.67–1.17) mEq/L ($P < 0.001$ for all changes) Week 4-week 52: statistically significant mean decreases in serum K + levels were observed at each monthly point in patients with mild and moderate HK	Difference in the proportion of patients remaining on spironolactone at week 12: 66% of patients in the placebo group and 86% of patients in the patiromer group remained on spironolactone (between-group difference 19.5%, 95% CI 10.0–29.0; $P < 0.0001$)	The adjusted mean change in K + was + 0.03 mmol/L in the patiromer group and + 0.13 mmol/L in the placebo group [difference in the adjusted mean change between patiromer and placebo: − 0.10 mmol/L (95% CI − 0.13, 0.07); $P < 0.001$] Risk of HK > 5.5 mmol/L (HR 0.63; 95% CI 0.45, 0.87; $P = 0.006$) and reduction of MRA dose (HR 0.62; 95% CI 0.45, 0.87; $P = 0.006$) were lower with patiromer HK-related morbidity-adjusted events (win ratio 1.53, $P < 0.001$) and total RAASi use score (win ratio 1.25, $P = 0.048$) favored the patiromer arm
Adverse effects	Most common adverse effects in the patiromer group: - gastrointestinal disorders (flatulence, diarrhea, constipation, and vomiting) (21% versus 6% in the placebo group)	Most common adverse effects: ITP: - mild-to-moderate constipation (11%) RWP: - supraventricular extrasystoles (4% versus 2% in the placebo group) - mild-to-moderate constipation, diarrhea and nausea (4% versus 0% in the placebo group)	Most common adverse effects: - hypomagnesemia (7.2%) - mild-to-moderate constipation (6.3%) - hypokalemia (< 3.5 mEq/L) (5.6%)	Adverse events were similar in both groups except for HK leading to the discontinuation of treatment which was higher in the placebo group (7% versus 1% in the patiromer group)	Most common adverse effects in the patiromer group: - diarrhea (4.3% versus 3.4% in the placebo group) - constipation (2.5% versus 1.1% in the placebo group)
Comments	55% of the patients had HF + CKD with eGFR < 60 mL/min	97% of the patients had hypertension; 57% had type 2 diabetes, 42% had HF, and 25% had had a myocardial infarction	All patients had hypertension and type 2 diabetes; 65% had stage 3 CKD and 22% had stage 4 CKD; 35% had HF	45% of the patients had a history of HF and 49.5% of diabetes	42.4% of the patients had Stage 3 CKD, and 40.5% had diabetes

ACEI ACE inhibitors, *ARB* angiotensin receptor blockers, *ARNI* angiotensin receptor neprilysin inhibitors, *CI* confidence interval, *CKD* chronic kidney disease, *ED* emergency department, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *ESRD* End-stage renal disease, *h* hours, *HD* hemodialysis, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HK* hyperkalemia, *HR* hazard ratio, *K+*, potassium, *MRA* mineralocorticoid receptor antagonists, *OD* odds ratio, *RAASi* renin–angiotensin–aldosterone system inhibitors, *SZC* sodium zirconium cyclosilicate.

Table 3 Summary of sodium zirconium cyclosilicate clinical studies for the treatment of hyperkalemia

	HARMONIZE (NCT02088073) [80]	Packham et al. (NCT01737697) [79]	PRIORITIZE-HF (NCT03532009) [78]	DIALIZE (NCT03303521) [89]	ENERGIZE (NCT03337477) [60]
Mechanism of action	SZC	SZC	SZC	SZC	SZC
Study design	Phase 3, randomized, double-blind, placebo-controlled	Phase 3, randomized, double-blind, placebo-controlled	Phase 2, randomized, double-blind, placebo-controlled	Phase 3b, randomized, double-blind, placebo-controlled	Phase 2, randomized, double-blind, placebo-controlled
Population	Outpatients with HK	Outpatients with HK	Patients with HFrEF	Patients with ESRD	ED patients with blood potassium ≥ 5.8 mmol/L
Regimen	Initial phase: SZC 10 g 3 × daily Maintenance phase: SZC 5–15 g/day or placebo	Initial phase:1.25 g, 2.5 g, 5 g, or 10 g of SZC or placebo, administered 3 × daily for the initial 48 h Maintenance phase: Patients in the SZC group assigned in a 1:1 ratio to receive either original SZC dose or placebo 1 × on days 3–14. Patients assigned to the placebo group in the initial phase were randomly assigned to receive either 1.25 g or 2.5 g of SZC	SZC 5 g or placebo once daily for 12 weeks. Doses of study medication and RAAS inhibitors were titrated during the treatment period	Patients were randomized 1:1 to receive orally a starting dose of SZC 5 g or placebo once daily on non-dialysis days Doses were titrated in 5 g increments to a maximum dose of 15 g once daily on non-dialysis days	Patients were randomized 1:1 to receive SZC 10 g or placebo, up to three times during a 10-h period, with insulin and glucose
Previous treatment	70% treated with RAAS inhibitors	66.7% patients were receiving RAAS inhibitors	ACEI (48.3%) ARB (34.1%) Sacubitril-valsartan (16.5%) MRA (18.7%) Diuretic (85.2%) Beta-blocker (91.2%)	HD three times weekly ≥ 3 months before randomization	ACE-I (22.9%) and ARB (12.9%)
Sample size	$n = 258$ initial phase $n = 237$ maintenance phase	$n = 754$ initial phase $n = 543$ maintenance phase	182	196	70
Median age (± SD) (years)	64.0 (12.7)	65.7 (12.2)	71.9 (8.4)	58.1	59 (13.8)
Baseline potassium levels mmol/L (± SD)	5.6 (0.4)	5.0–5.3 (56.7%) 5.4–5.5 (20.2%) 5.6–6.5 (23.1%)	4.86 (0.35)	5.5–5.9 (pre-dialysis)	6.5 (0.70)
Follow-up	Initial phase: 48 h Maintenance phase: 28 days	Initial phase: 48 h Maintenance phase: 14 days	3 months	1-week screening period 8-week treatment period 2-week follow-up period	24 h

Table 3 (continued)

	HARMONIZE (NCT02088073) [80]	Packham et al. (NCT01737697) [79]	PRIORITIZE-HF (NCT03532009) [78]	DIALIZE (NCT03303521) [89]	ENERGIZE (NCT03337477) [60]
Primary outcome	Initial phase: serum K + levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 h 84% of patients (95% CI, 79–88%) achieved normokalemia by 24 h and 98% (95% CI, 96–99%) by 48 h Maintenance phase: serum K + was significantly lower during days 8–29 with all 3 SZC doses versus placebo (4.8 mEq/L [95% CI, 4.6–4.9], 4.5 mEq/L [95% CI, 4.4–4.6], and 4.4 mEq/L [95% CI, 4.3–4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0–5.2] for placebo; $P < 0.001$ for all comparisons)	Change in K + at 48 h: Ranged from − 0.16 to − 0.30% for SZC groups compared to − 0.09% for placebo ($P < 0.001$ for each comparison) The mean reduction from baseline at 1 h after the first 10 g dose of SZC was 0.11 mmol/L (95% CI, − 0.17 to − 0.05), as compared with an increase of 0.01 mmol/L (95% CI, − 0.05 to 0.07) in the placebo group ($P = 0.009$) Normokalemia was maintained during 12 days of maintenance therapy	There was no statistically significant difference in the distribution of patients by RAAS inhibitor treatment categories at 3 months ($P = 0.43$). The proportion of patients at target MRA dose was numerically higher in the SZC group (56.4%) compared with the placebo group (47.0%) At end of treatment, 80.4% of patients in the SZC group were normokalemic compared with 63.6% of patients in the placebo group	Responders: during the 4-week evaluation period, maintained serum K + of 4.0–5.0 mmol/L during ≥ 3 of 4 HD treatments and who did not require rescue therapy 41.2% patients receiving SZC were responders compared with 1.0% of patients receiving placebo ($P < 0.001$)	The least squares mean (± SD) K + change from baseline to 4 h was − 0.41 (± 0.11) mmol/L and − 0.27 (± 0.10) mmol/L with SZC and placebo, respectively (difference = –0.13 mmol/L; 95% CI, 0.44–0.17). A greater reduction in mean (± SD) K + from baseline occurred with SZC compared with placebo at 2 h: –0.72 (± 0.12) versus –0.36 (± 0.11) mmol/L respectively. A numerically lower proportion of patients in the SZC group required additional K + -lowering therapy due to HK at 0 to 4 h versus placebo (15.6% versus 30.6%, respectively; OD = 0.40; 95% CI, 0.09–1.77)
Adverse effects	Adverse effects were more prominent in the SZC = 15 g group: - anemia (5.4% versus 0% in the placebo group) - edema (14.3% versus 2.4% in the placebo group) - hypokalemia (10.7% versus 0% in the placebo group) - nasopharyngitis (2.4% versus 1.2% in the placebo)	Adverse effects were mainly observed in the maintenance phase with SZC = 10 g: - gastrointestinal disorders (4.8% versus 0% in the placebo group) - cardiac disorders (3.2% versus 1.6% in the placebo group)	Most common adverse effects in the SZ 101. C group: - Edema (3.3% patients versus 1.1% in the placebo group) - worsening HF (12.1% versus 5.6% in the placebo group	Most common adverse effects in the SZC group: - gastrointestinal disorders (19.8% versus 17.2% patients in the placebo group) - infections (12.5% versus 9.1% patients in the placebo group)	Most common adverse effects in the SZC group: Clinically significant hypoglycemia (13.8% versus 9.1% of patients in the placebo group) between 0 and 24 h

Table 3 (continued)

	HARMONIZE (NCT02088073) [80]	Packham et al. (NCT01737697) [79]	PRIORITIZE-HF (NCT03532009) [78]	DIALIZE (NCT03303521) [89]	ENERGIZE (NCT03337477) [60]
Comments	66% of the patients had CKD, 36% had HF and 66% had diabetes	61.5% of the patients had CKD, 59.9% had diabetes, and 39.8% had a history of HF	Study was terminated prematurely due to COVID-19 and did not demonstrate a statistically significant increase in the intensity of RAAS inhibitor therapies with the potassium-reducing agent SZC compared with placebo	Mean dialysis history of 7.9 years	35.7% of the patients had CKD, 25.7% had coronary artery disease, 2.9% had myocardial infarction and 30% had diabetes At 1 h after the start of dosing, the least squares mean (SD) change from baseline in K + was similar between groups: –0.67 (0.12) versus –0.67 (0.11) mmol/L for SZC and placebo, respectively

ACEI ACE inhibitors, *ARB* angiotensin receptor blockers, *ARNI* angiotensin receptor neprilysin inhibitors, *CI* confidence interval, *CKD* chronic kidney disease, *ED* emergency department, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *h* hours, *HD* hemodialysis, *HF* heart failure, *HFrEF* heart failure with reduced ejection fraction, *HK* hyperkalemia, *HR* hazard ratio, *K* + potassium, *MRA* mineralocorticoid receptor antagonists, OD odds ratio, *RAASi* renin–angiotensin–aldosterone system inhibitors, *SZC* sodium zirconium cyclosilicate.

binders for situations where newer agents are unavailable or contraindicated.

Recent advancements in the research of HK have introduced new potassium binders, offering more effective and tolerable options for patients (Table 1). Patiromer and SZC are the latest additions, designed to lower serum potassium levels by binding potassium in the gastrointestinal tract and facilitating its excretion through the stool [45, 49, 53–55]. These innovative agents have demonstrated potential in clinical trials [53, 55], delivering sustained reduction in potassium levels with a favorable safety profile. This makes them well-suited for long-term HK management, particularly in patients with CKD or HF undergoing high doses of RAASi [56, 57]. Their introduction marks a significant improvement in the therapeutic landscape, offering clinicians additional resources to manage HK more effectively while minimizing patient discomfort and adverse effects.

Patiromer

Patiromer is an organic, sodium-free, non-absorbed polymer designed to exchange potassium for calcium throughout the gastrointestinal tract but mostly in the colon [56]. Clinical studies have demonstrated patiromer efficacy in reducing serum potassium levels (Table 2), with a favorable safety profile that includes fewer gastrointestinal side effects compared to traditional binders like SPS [63–65]. Additionally, patiromer minimal systemic absorption makes it a convenient option for long-term use [66] [64]. Its ability to lower potassium levels without significantly altering other electrolytes contributes to its tolerability and suitability for chronic management [56, 66, 67].

Real-world clinical data from patients receiving chronic hemodialysis demonstrated that the relative proportion of patients with severe HK (≥ 6.0 mmol/L) was reduced by approximately 50% following patiromer initiation [68]. Concurrently with the observed reductions in serum potassium, the results regarding dose and duration of use indicated the healthcare providers' intention for chronic patiromer use [68]. Additionally, long-term patiromer was recently shown to be associated with a lower risk of all-cause mortality among patients with CKD and HK [69]. Patiromer has also demonstrated the ability to support the ongoing use of RAASi therapy [70, 71], fundamental for managing CKD and HF. Moreover, it has shown high effectiveness in potassium reduction, with 80% of patients maintaining RAASi therapy after 6 months of patiromer initiation, thereby aligning with guideline-driven medication objectives [72].

Until now, formal studies on patiromer in emergency setting for acute HK have been lacking [65]. However, in an open-label study aimed at determining the time to onset of action, a significant reduction in serum potassium levels

Table 4 Misconceptions about the use of novel potassium binders identified by the multidisciplinary expert panel in their clinical practice

Misconceptions	Facts	References
My patients do not have HK	The prevalence of HK is notably high among patients with CKD and HF, underscoring the critical need for vigilant monitoring and management in these populations	[30, 91, 92]
I control potassium levels well with diet and diuretics	General dietary potassium restriction is not an adequate strategy to manage HK and diuretics are not ideal for the long-term management of HK	[4, 7, 48]
Resins are effective and well tolerated	SPS/CPS is not well tolerated and may cause severe gastrointestinal adverse events These resins are not recommended by KDIGO guidelines to control HK	[2, 4, 93]
My patients are treated with optimal doses of RAASi, according to current guidelines	Despite adherence to current guidelines for RAASi dosing, real-world clinical practice often reveals suboptimal treatment levels, due to HK as a limiting factor	[2, 4, 11, 92]
Non-steroidal MRAs exclude the need to use potassium binders	While non-steroidal MRAs can help manage hyperkalemia, they do not universally eliminate the need for potassium binders, as individual patient responses and clinical circumstances may still necessitate their use	[94]
Potassium binders can be used as a substitute for emergency therapy	Despite the absence of approval for acute HK, potassium binders such as patiromer and SZC are recommended following initial emergency interventions with IV calcium, IV insulin-glucose, and nebulized salbutamol The earliest onset of action studied is 1 h for SZC and 2 h for patiromer Both agents require administration intervals to avoid drug interactions: 2 h for SZC and 3 h for patiromer	[15, 60, 74, 75]
Patiromer has no data in dialysis	Recent studies have demonstrated its efficacy and safety in managing HK among dialysis patients	[68, 73]
Metabolic acidosis is an obstacle to the use of patiromer	Metabolic acidosis is not currently described as an adverse effect of patiromer treatment, but it is a frequent condition in CKD patients and patients under RAASi treatment To control metabolic acidosis, it is recommended to use oral sodium bicarbonate SZC increases serum bicarbonate, and this mechanism of action may potentially result in benefits dependent on corrected metabolic acidosis	[4, 95–97]
Hypomagnesemia is an obstacle to the use of patiromer	In clinical trials, hypomagnesemia and "blood magnesium decreased" were observed in 5.3% and 0.8% of patients, respectively. However, the global pharmacovigilance database reported much lower rates of 0.02% and 0.16%, respectively Although hypomagnesaemia related to patiromer is mild and does not carry cardiac arrhythmias, it is recommended to monitor Mg levels and to supplement in cases with Mg < 1.5 mg/dL	[95, 98]
Sodium does not pose an additional risk in the management of renal/ cardiovascular patients	Sodium poses additional risks in the management of renal and cardiovascular patients; the sodium content in SZC, although low (80 mg/g), must be carefully considered to avoid exacerbating hypertension and fluid retention	[88, 99, 100]

CPS calcium polystyrene sulfonate, *HK* hyperkalemia, *KDIGO* Kidney Disease: Improving Global Outcomes *RAASi* renin–angiotensin–aldosterone system inhibitors, *SPS* sodium polystyrene sulfonate, *SZC* sodium zirconium cyclosilicate.

among hyperkalemic patients was observed within 4 to 7 h [73], suggesting its utility primarily in the context of chronic HK. Nevertheless, a pilot investigation targeting severe and acute HK revealed that a single oral dose of 25.2 g of patiromer led to a statistically significant reduction in serum potassium within 2 h, indicating a potential role in acute HK management [74]. In agreement, Di Palo et al. conducted a retrospective cohort study evaluating patiromer therapy for HK in an acute care setting [75]. Their findings indicated a mean potassium reduction of 0.50 (SD 0.56) mmol/L ($p < 0.001$) within 0 to 6 h following a single dose of patiromer administration in patients with acute HK [75].

Sodium zirconium cyclosilicate

SZC is an insoluble, non-absorbable, non-polymer inorganic material that selectively exchanges sodium and hydrogen ions for potassium ions in the gastrointestinal tract, thereby reducing serum potassium levels through fecal excretion [78]. One clinical trial demonstrated that SZC has an onset of action within 1 h (Table 3) [79]. However, potassium levels obtained less than 6 h after administration of a potassium-binder can result from concomitant HK therapies that temporarily shift potassium intracellularly [45]. In fact, a pilot randomized clinical trial explored the efficacy of SZC with insulin and glucose as HK treatment in the emergency department and reported that at 1 h after the start of dosing, the least squares mean change from baseline in potassium was similar between the SZC group (-0.67 ± 0.12) and the placebo group (-0.67 ± 0.11) mmol/L [60].

Several clinical studies have reported sustained potassium-lowering effects of SZC over longer durations [79–82]. It is well-tolerated, with a safety profile that includes mild gastrointestinal side effects, such as edema, which is generally manageable [81]. Similarly to patiromer, minimal systemic absorption enhances patient compliance and convenience [80]. The efficacy of SZC in lowering potassium levels has been shown to be consistent across different populations, including those with CKD [81], HF [78, 82], hemodialysis patients [83, 84], and those under RAASi [82, 85–87]. In an observational multicountry cohort study, patients with CKD and/or HF treated with SZC were significantly more likely to maintain guideline-accordant RAASi therapy at 6 months following HK compared to patients under no potassium binder treatment [87]. Recently, a real-world study showed that nearly 80% of patients with ESKD, CKD, and CKD with diabetes who initiated SZC for HK were able to optimize their RAASi therapy [85]. A recent retrospective study with CKD patients also demonstrated the benefit of SZC in reducing mortality and HK-associated hospitalizations, albeit the high RAASi persistence rate in the SZC group could have contributed to the better management of CKD and lower events rate [86]. Another real-world study found that SZC treatment might be associated with an increased risk of hospitalizations for HF in comparison to patiromer [88]. Therefore, the selection of an optimal approach to the management of HK should consider the potential impact of the sodium load on patients.

Conclusion and future perspectives

The advent of novel potassium binders such as patiromer and SZC represents a significant advancement in the management of HK, offering new therapeutic options that enhance patient outcomes and safety profiles. These agents have demonstrated efficacy in lowering serum potassium levels and maintaining long-term normokalemia, providing critical support in the management of patients with CKD, HF, and other conditions predisposed to HK, as well as optimizing RAASi therapy. Despite their efficacy, there is a pressing need for extensive long-term studies to evaluate their safety profiles, potential side effects, and impacts on patient quality of life.

Future research on HK treatment should focus on optimizing the use of patiromer and SZC through randomized controlled trials to evaluate their impact on mortality in patients with HK. Investigations should aim to establish standardized dosing regimens tailored to individual patient characteristics, such as comorbid conditions and concurrent medications. Comparative studies are necessary to determine the relative effectiveness and cost-efficiency of patiromer versus SZC in diverse patient populations. Research should also explore the mechanisms by which these agents interact with other treatments for HK and their role in comprehensive disease management strategies (Table 4).

Particularly in the acute HK setting, further research should explore the implementation of protocols for treatment, including novel potassium binders. The ongoing KBindER randomized study, expected to be completed by December 2024, aims to compare oral potassium binders in the treatment of acute HK and will hopefully inform decision-making guidelines on this matter [46]. Another important field of research is to determine the efficacy of recommending dietary restriction of potassium-rich foods in patients with CKD or HF, specifically from plant-based sources, as these foods also provide cardiometabolic health benefits [48, 90]. Clinical trials are needed to test the validity of dietary potassium intake from different food sources, both alone and in combination with gut-targeted interventions, for optimal potassium management.

Concomitant to the need for well-designed clinical trials, conducting and reporting data from real-world settings is crucial to ensure the true long-term effectiveness and

safety of patiromer and SZC. A holistic approach involving the collective expertise of cardiologists, nephrologists, internists, and nutritionists is essential for optimizing HK management and improving the overall quality of care for patients. Clear, evidence-based communication is vital to guide healthcare providers in selecting the most appropriate therapy based on individual patient needs and clinical scenarios, ensuring both effective and safe management of HK across different settings.

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Authors and Affiliations

Cândida Fonseca[1,2] · Cristina Garagarza[3,4] · Gil Silva[5] · Graça Caires[6] · Irene Marques[7,8] · José António Lopes[4,9] · Patrícia Branco[10] · Rui Alves[11,12] · Aníbal Ferreira[2,13]

✉ Cândida Fonseca
mcandidafonseca@gmail.com

1 Heart Failure Clinic, Department of Internal Medicine, Unidade Local de Saúde Lisboa Ocidental (ULSLO), Lisbon, Portugal

2 NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisbon, Portugal

3 Department of Nutrition, Nephrocare, 1750-233 Lisbon, Portugal

4 Faculty of Medicine, University of Lisbon, 1649-028 Lisbon, Portugal

5 SESARAM, Department of Nephrology, 9004-514 Funchal, Madeira, Portugal

6 SESARAM, Department of Cardiology, 9004-514 Funchal, Madeira, Portugal

7 Department of Internal Medicine, Hospital de Santo António, Unidade Local de Saúde Santo António, 4099-001 Porto, Portugal

8 Unidade Multidisciplinar de Investigação Biomédica (UMIB) – Instituto de Ciências Biomédicas de Abel Salazar (ICBAS), University of Porto, 4050-313 Porto, Portugal

9 Department of Nephrology and Kidney Transplantation, Unidade Local de Saúde Santa Maria, 1649-035 Lisbon, Portugal

10 Department of Nephrology, Hospital Beatriz Ângelo, Unidade Local de Saúde de Loures-Odivelas, 2674-514 Loures, Portugal

11 Department of Nephrology, Unidade Local de Saúde Coimbra, 3004-561 Coimbra, Portugal

12 Faculty of Medicine, University of Coimbra, 3000-548 Coimbra, Portugal

13 Department of Nephrology, Hospital Curry Cabral, Unidade Local de Saúde São José, Lisbon, Portugal